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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow CM19 5AW (GB). KING, Francis, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Andrian [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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(57) Abstract

Novel sulphonamide derivatives having CNS activity, processes for their preparation and their use as medicaments.

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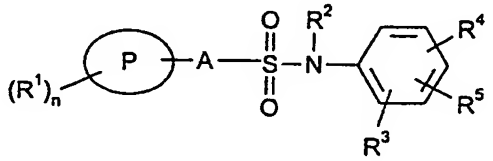
SULPHONAMIDE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS MEDICAMENTS

This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

EPA 0 021 580 and EPA 0 076 072 describe sulphonamide derivatives which are disclosed as having antiarrhythmic activity. A structurally distinct class of compounds has now been discovered, which have been found to have $5HT_6$ receptor antagonist activity. $5HT_6$ receptor antagonists are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory enhancement e.g. for the treatment Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome).

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched. Preferred alkyl groups are generally methyl and ethyl. As used herein the term aryl includes optionally substituted phenyl and naphthyl.

When P is a bicyclic heterocyclic ring suitable examples include benzothiophene, quinoline or isoquinoline. When P is a 5 to 7-membered heterocyclic ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrrolidinyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom. Suitable substituents for these rings include R^5 groups as defined above.

Preferably P is phenyl, thiophene, benzothiophene or naphthyl.

Preferably A is a single bond, an ethylene group or a -CH=CH- group. Most preferably A is a single bond.

When R^1 is a heterocyclic group suitable examples include those listed above. Preferably R^1 is halogen or C_{1-6}alkyl optionally substituted by one or more halogen atoms, for example methyl or trifluoromethyl.

Preferably n is 0, 1, 2 or 3, particularly 1 or 2.

Suitably R^2 is hydrogen or C_{1-6} alkyl. Preferably R^2 is hydrogen.

It will be appreciated that when R^3/R^5 groups are linked together the two groups must be attached to adjacent carbon atoms of the phenyl ring. Preferably R^3 is a group R^5, in particular hydrogen.

Preferably R^4 is meta with respect to the sulphonamide linkage. Preferably X is a bond, p is 0 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring. The heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen atom. Optional substituents for these rings, which can be present on carbon and/or nitrogen atoms, include C_{1-6}alkyl, in

particular methyl. More preferably R^4 is N-piperazine optionally substituted by C_{1-6}alkyl, particularly unsubstituted piperazine.

Preferably R^5 is C_{1-6}alkoxy, most preferably methoxy. Preferably R^5 is para with respect to the sulphonamide linkage.

A preferred meaning for P-A is benzo[b]thiophen-2-yl or benzo[b]thiophen-3-yl optionally substituted by one or two R^1 groups, especially 5-chloro-3-methyl-benzo[2]thiophen-2-yl.

Particular compounds of the invention include:

4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-5-(pyridin-2-yl)-2-thiophenesulfonamide,
2,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-thiophenesulfonamide,
4-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzylsulfonamide,
2-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-*trans*-styrenesulfonamide,
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-[2,1,3]benzothiadiazole-4-sulfonamide,
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-2-benzothiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-5-nitro-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-trifluoromethyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-trifluoromethyl-benzenesulfonamide,

2,5-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
4-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-*tert*-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Isopropyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-*tert*-Amyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-trifluoromethoxy-benzenesulfonamide,
4-n-Butoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methylbenzenesulfonamide,
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-naphthalenesulfonamide,
5-(Dimethylamino)-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide,
4-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-benzenesulfonamide,
4-Methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-n-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Amino-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
2-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
2,3,4-Trichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,5-dimethyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzenesulfonamide,
2,5-Dibromo-3,6-difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,3,5,6-tetramethyl-benzenesulfonamide,
5-Chloro-2-methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
3-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3,4-Difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,

4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-nitro-benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-8-quinolinesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenylbenzenesulfonamide,
3,4-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,5-dimethyl-4-isoxazolesulfonamide,
4-Bromo-N-[4-methoxy-3-(4-ethylpiperazin-1-yl)phenyl]benzenesulfonamide,
2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
5-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-benzenesulfonamide,
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide,
5-Chloronaphthalene-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
4-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
7-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
Benzofuran-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
1-Methyl-1H-indole-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Pyridin-2-ylthiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
N-(4-Methoxy-3-piperazin-1-ylphenyl)-3-trifluoromethylbenzenesulfonamide,
3-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3,5-Dimethylisoxazole-4-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
3,5-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
2,5-Dibromo-3,6-difluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
Naphthalene-1-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

2-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,.

2-Chloro-4-fluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

3-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

5-Chloronaphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,

4-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

2,5-Dichlorothiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide

4-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

1-Methyl-1H-indole-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

Benzofuran-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

Naphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,

5-Chloronaphthalene-1-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,

4-Chloro-2,5-dimethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-4-methyl-benzenesulfonamide,

2-Trifluoromethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

4-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

4-tert-Butyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,

Naphthalene-1-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

Thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

5-Chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

5-Pyridin-2-ylthiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

2,5-Dichlorothiophene-3-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

4-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

3-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

4-Chloro-2,5-dimethyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

Naphthalene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide.

3-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,

3,5-Dichloro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,

4-*tert*-Butyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,

2,5-Dibromo-3,6-difluoro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,

2,5-Dibromo-3,6-difluoro-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzenesulfonamide,

4-Chloro-2,5-dimethyl-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzenesulfonamide,

5-Chloro-3-methyl benzo [b] thiophene-2-sulphonic acid [3-(4-cyclopropylmethyl-piperazin-1-yl)-4-methoxy-phenyl] amide,

5-Chloro-3-methyl benzo [b] thiophene-2-sulphonic acid [3-(4-benzyl-piperazin-1-yl)-4-methoxy-phenyl]-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-benzyloxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-ethoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-isopropoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-methoxy-3-(1-methyl-pyrrolidin-3-yloxy)-phenyl]-amide,

Naphthalene-2-sulfonic acid [2-bromo-5-(4-methylpiperazin-1-yl)phenyl]amide

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-chloro-3-(4-methylpiperazin-1-yl)phenyl]amide,

Naphthalene-2-sulfonic acid [4-bromo-3-(4-methylpiperazin-1-yl)phenyl]amide,

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[3-(2-dimethylaminoethoxy)-4-iodophenyl]amide,

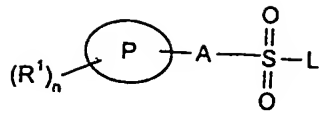
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-dimethylaminoethyl)-2,3-dihydro-1H-indol-6-yl]amide,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[4-methoxy-2-methyl-3-(4-methylpiperazin-1-yl)phenyl]amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[2-(2-hydroxyethyl)-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-4-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole hydrochloride,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amide,
4-Bromo-N-[4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]benzenesulfonamide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]amide
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methylpiperidin-4-yl)phenyl]amide
Naphthalene-2-sulfonic acid [3-(4-methylpiperazin-1-yl)phenyl]amide
and pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

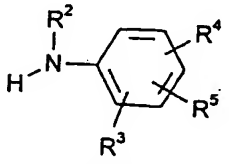
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):



(II)

in which R^1, n, P, and A are as defined in formula (I) or protected derivatives thereof and L is a leaving group with a compound of formula (III):



(III)

in which R^2, R^3, R^4 and R^5 are as defined in formula (I) or protected derivatives thereof and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

Suitable leaving groups include halogen, in particular chloro. The reaction of a compounds of formulae (II) and (III) is carried out by mixing the two reagents together, optionally in an inert solvent such as acetone. Such a reaction may be carried out in the presence of base.

Those skilled in the art will appreciate that it may be necesary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981). For example, suitable protecting groups for the piperazine group include BOC, $COCCl_3$, $COCF_3$ and methyl the latter of which may be removed by treatment with 1-chloroethyl chloroformate according to standard procedures.

N-substituted piperazines can be prepared by acylation or alkylation of the appropriate NH-piperazine compound according to standard procedures.

Compounds of formulae (II) and (III) are commercially available or may be prepared according to known methods or analogous to known methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_6$ receptor antagonist activity and are believed to be of potential use in the

treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease (cognitive memory enhancement), sleep disorders (including disturbances of Circadian Rythym), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-(2-Methoxy-5-nitrophenyl)piperazine (D1)

A solution of 5M sulphuric acid (114ml) was added over 0.3h to 1-(2-methoxyphenyl)piperazine (110g) at 0°C with stirring. To the ice-cooled stirred slurry was then added, over 1.75h, concentrated sulphuric acid (560ml) and the temperature was maintained for a further 1.5h. Potassium nitrate (71.5g) was then added portionwise over 1.5h to the stirred, cold, viscous mixture which was then left to stand for 18h. The solution was poured onto ice (2Kg) and the resulting cooled mixture brought to pH 12 by the addition of 40% sodium hydroxide solution. The

oily mixture was extracted with ethyl acetate (2 x 2L) and the combined organic extracts were washed with water (3L), dried (Na_2SO_4), concentrated to a residue which was stirred with diethyl ether (700ml) to give the title compound (D1) as a yellow solid, m.p. 84-87°C (95g, 70%). MH^+238.

Description 2

4-*tert*-Butoxycarbonyl-1-(2-methoxy-5-nitrophenyl)piperazine (D2)

To a stirred heterogeneous solution of 1-(2-methoxy-5-nitrophenyl)piperazine (D1) (99.2g) in tetrahydrofuran (1.1L) and water (1.1L) was added a solution of di-*tert*-butyldicarbonate (91.3g) in tetrahydrofuran (300ml) over 0.5h. Potassium carbonate (60.7g) was then added in portions over 0.5h and the mixture was stirred at ambient temperature for 18h. The whole was concentrated to remove the organic solvent and the resulting mixture was extracted with dichloromethane (2 x 1L). The combined organic phases were washed with water (1L), dried (Na_2SO_4) and concentrated to a residue which was stirred with diethyl ether (500ml) and hexane (750ml) to afford the title compound (D2)as a yellow solid, m.p. 136-7°C (125g, 89%). MH^+338.

Description 3

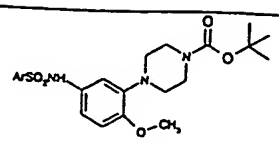
4-*tert*-Butoxycarbonyl-1-(5-amino-2-methoxyphenyl)piperazine (D3)

A slurry of 10% palladium on carbon (10g) in a solution of 4-*tert*-butoxycarbonyl-1-(2-methoxy-5-nitrophenyl)piperazine (D2) (124.5g) in ethanol (3.5L) and water (50ml) was stirred with hydrogen at ambient temperature and atmospheric pressure for 18h. The reaction mixture was filtered and the filtrate concentrated to afford the title compound (D3) as a gum (112g, 99%). MH^+ 308.

Description 4-14

General Preparation of N-[4-methoxy-3-(4-*t*-butoxycarbonyl-1-piperazinyl)phenyl] arylsulfonamides (D4-D14)

A solution of 4-*t*-butoxycarbonyl-1-(5-amino-2-methoxyphenyl)piperazine (D3) (15.6mmol), diisopropylethylamine (15.6mmol) and the appropriate aryl sulfonyl chloride (15.6mmol) in dichloromethane (100ml) was stirred at room temperature for 18h. The mixture was concentrated and the residue chromatographed on silica gel eluting with a dichloromethane/methanol gradient to give the following pure title products.

	MS(MH+)
2-Chloro-4-fluoro-N-[4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]benzenesulfonamide (D4)	*
3-Bromo-N-[4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]benzenesulfonamide (D5)	*
3-Chloro-N-[4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]benzenesulfonamide (D6)	*
4-Bromo-5-chlorothiophene-2-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl] amide (D7)	*
2,5-Dichlorothiophene-3-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]amide (D8)	*
4-Bromo-N-[4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]benzenesulfonamide (D9)	526/528
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl] amide (D10)	552/554
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl] amide (D11)	552/554
Benzofuran-2-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl] amide (D12)	488
1-Methyl-1H-indole-2-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl] amide (D13)	501
5-Chloronaphthalene-2-sulfonic acid [4-methoxy-3-(4-t-butoxycarbonyl-1-piperazinyl)phenyl]amide (D14)	*

* Intermediate used crude without isolation

Description 10

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl)amide (D10)

Pyridine (60ml) was added to a stirred solution of 4-*tert*-butoxycarbonyl-1-(5-amino-2-methoxyphenyl)piperazine (D3) (112g) in dichloromethane (1L) at ambient temperature under argon. To this solution was added over 0.75h a solution of 5-

Chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (102.5g) in dichloromethane (2.1L) and the purple solution was stirred for 18h. The mixture was then washed with 1M hydrochloric acid solution (3L), water (3L), dried (Na_2SO_4), and concentrated to a foam which was stirred with acetone (800ml) and water (800ml) to afford the title compound (D10) as a maroon solid, m.p. 100-103°C (194.9g, 97%). MH^+ 552/554.

Description 15

1-(2-Methoxy-5-nitrophenyl)-4-trichloroacetylpiperazine (D15)

A solution of 5-nitro-1-(2-methoxyphenyl)piperazine (D1) (44g) in dichloromethane (300ml) was added to a stirred solution of trichloroacetylchloride (32ml) in dichloromethane (200ml) over 0.25h. After 3hrs, the reaction mixture was concentrated and the residue recrystallised from chloroform to yield the title compound (D15) as a yellow solid (43g, 61%). Found MH^+ 382/384.

Description 16

1-(5-Amino-2-methoxyphenyl)-4-trichloroacetylpiperazine (D16)

A solution of stannous chloride dihydrate (27g) in concentrated HCl (60ml) was slowly added to a stirred suspension of 1-(2-methoxy-5-nitrophenyl)-4-trichloroacetylpiperazine (D15) (15g) in concentrated HCl/ethanol (1:2, 120ml). After 24hrs, the mixture was filtered, diluted with dichloromethane (600ml) and basified with Na_2CO_3 solution. The layers were separated, the organic phase dried, concentrated to 1/3 the volume and acidified with 1M ethereal HCl solution to afford the title compound (D16) as a green solid (2.5g, 15%). Found MH^+ 352.

Description 17

Cyclopropyl-[4-(2-methoxy-5-nitrophenyl)-piperazin-1-yl]methanone (D17)

To a solution of 1-(2-methoxy-5-nitrophenyl)-piperazine (500mg, 2.1mmol) in dichloromethane (50ml) at 0°C under argon was added triethylamine (0.59ml, 4.2mmol) and cyclopropane carbonyl chloride (2.1mmol). Stirring was continued for 12 hrs. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous $NaHCO_3$ and dichloromethane. The organic layer was dried over sodium sulphate and concentrated *in vacuo* to give the title compound (D17) in 90% yield. Found MH^+ 306.

Description 18

[4-(2-Methoxy-5-nitrophenyl)-piperazin-1-yl] phenyl methanone (D18)

The title compound was prepared in 85% yield using the procedure outlined in D17 using benzoyl chloride. Found MH^+ 342.

Description 19

[4-(5-Amino-2-methoxy-phenyl)-piperazin-1-yl] cyclopropyl methanone (D19)

A solution of the cyclopropyl-[4-(2-methoxy-5-nitrophenyl)-piperazin-1-yl]methanone (D17) (1.8mmol) in ethanol was hydrogenated over 10% Palladium on charcoal catalyst for 2hrs at room temperature to give the title compound in 91% yield. Found MH^+ 276.

Description 20

[4-(5-Amino-2-methoxy-phenyl)-piperazin-1-yl] phenyl methanone (D20)

The title compound was prepared in 95% yield using the procedure outlined in D19. Found MH^+ 312

Description 21

3-(4-Cyclopropylmethyl-piperazin-1-yl)-4-methoxy-phenylamine (D21)

To a solution of [4-(5-amino-2-methoxy-phenyl)-piperazin-1-yl] cyclopropyl methanone (D19) (1.6mmol) in dry THF (10ml) under argon was added $LiAlH_4$ (240mg, 6.4mmol). The resulting mixture was heated to reflux for 12hrs and cooled before quenching with water (0.25ml), 10% aqueous NaOH (0.25ml) and finally water (0.75ml). Filtration through celite and concentration *in vacuo* afforded the title compound (D21) in 75% yield. Found MH^+ 262.

Description 22

3-(4-Benzyl-piperazin-1-yl)-4-methoxy-phenylamine (D22)

The title compound was prepared in 76% yield using the procedure outlined in D21. Found MH^+ 298.

Description 23

Methane sulphonic acid 1-methyl pyrrolidin-3-yl ester (D23)

To a solution of 1-methyl-pyrrolidin-3-ol (2.0g, 20mmol) and triethylamine (3ml, 22mmol) in dichloromethane (25ml) at 0°C under argon was added methane sulphonyl chloride (2.4g, 21mmol). Stirring was continued at 0°C to room temperature for 1hr before partitioning between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated *in vacuo* to afford the crude mesylate (3.6g) which was used directly in the next step.

Description 24

3-(2-Methoxy-5-nitro-phenoxy)-1-methyl-pyrrolidine (D24)

A solution of 2-methoxy-5-nitro phenol (5.1g, 30mmol) in DMF (10ml) was added to sodium hydride (1.6g, 66mmol) under argon. After 1hr a solution of the crude mesylate (D23, 3.6g, 20mmol) in DMF (10ml) was added and the reaction mixture warmed to 50°C for 48hrs. The reaction was cooled, quenched with water and concentrated *in vacuo* before partitioning between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the title compound (D24). Found MH^+ 253.

Description 25

4-Methoxy-3-(1-methyl-pyrrolidin-3-yloxy)phenylamine (D25)

A solution of 3-(2-methoxy-5-nitro-phenoxy)-1-methyl-pyrrolidine (3.0g, 0.12mmol) in ethanol (50ml) was hydrogenated over 10% palladium on charcoal catalyst for 2hrs to afford the title compound (D25). Found MH^+ 223.

Description 26

1-(4-Bromo-3-nitrophenyl)-4-methylpiperazine (D26)

A solution of 1-methyl-4-(3-nitrophenyl)piperazine (EP0533267A) (1.0g; 4.5 mmol) in glacial acetic acid (25 ml) was treated with bromine (0.23 ml; 1 equivalent). The reaction mixture was stirred at 75° overnight, then cooled, filtered, and the yellow sticky solid was partitioned between potassium carbonate (aq) and 2% methanol in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to leave the title compound (D26) as a viscous orange oil (928 mg, 68%) MH^+=300/302.

Description 27

2-Bromo-5-(4-methylpiperazin-l-yl)phenylamine (D27)

A suspension of iron powder (1.77g, 31.6 mmol) in saturated aqueous ammonium chloride solution (140 ml) at 100°C, was treated dropwise with a solution of 1-(4-bromo-3-nitrophenyl)-4-methylpiperazine (D26) (3.54g, 11.8 mmol) in methanol (70 ml). The mixture was refluxed for a further 1h, and was then cooled and partitioned between water and 3% methanol in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. This was purified by chromatography on silica gel, eluting with methanol and dichloromethane to give the title compound (D27) as a white solid (2.18g, 68%) MH^+=270/272.

Description 28

2-Meth xy-6-methylphenylamine (D28)

A solution of 1-methoxy-3-methyl-2-nitrobenzene (15.04g, 0.09 mol) in ethanol (250 ml) was hydrogenated over 10% palladium on charcoal (4g) at atmospheric pressure and at room temperature, for 18h. The catalyst was removed by filtration, and the filtrate evaporated under reduced pressure to leave the title compound (D28) as an amber oil, which crystallised on standing (11.18g, 91%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 6.75-6.65 (m, 3H), 3.81 (s, 3H), 3.72 (br s, 2H), 2.19 (s, 3H).

Description 29

1-(2-Methoxy-6-methylphenyl)-4-methylpiperazine (D29)

A mixture of 2-methoxy-6-methylphenylamine (D28) (3.62g, 26.4 mmol), mechlorethamine hydrochloride (12.7g, 66 mmol) and potassium carbonate (15g) in chlorobenzene (90 ml) was refluxed under argon for 20 h. The mixture was cooled and filtered, and the filtrate evaporated under reduced pressure to leave the title compound (D29) as a red oil which slowly crystallised on standing (5.4g, 93%) MH^+=221.

Description 30

1-(6-Methoxy-2-methyl-3-nitrophenyl)-4-methylpiperazine (D30)

A solution of 1-(2-methoxy-6-methylphenyl)-4-methylpiperazine (D29) (6.2g, 28 mmol) in concentrated sulfuric acid (50 ml) was treated portionwise with potassium nitrate (3.3g, 33 mmol) over 5 mins, maintaining the temperature at 25-30°C. The mixture was stirred overnight at room temperature, then added to ice, and basified with 40% sodium hydroxide solution. The mixture was extracted with dichloromethane and the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give crude compound. Purification by chromatography on silica gel eluting with methanol and dichloromethane afforded the title compound (D30) (4.56g, 61%) MH^+=266.

Description 31

2-[3-Methoxy-2-(4-methylpiperazin-1-yl)-6-nitrophenyl]ethanol (D31)

A mixture of 1-(6-methoxy-2-methyl-3-nitrophenyl)-4-methylpiperazine (D30) (360 mg, 1.36 mmol), dry dimethylsulfoxide (3 ml), paraformaldehyde (82 mg, 2.72 mmol) and potassium tert-butoxide (52 mg, 0.46 mmol) was heated at 70-75°C for 30 h. After cooling, the mixture was partitioned between water and ethyl acetate. The organic phase was dried (Na_2SO_4) evaporated under reduced pressure and purified by

chromatography on silica gel, eluting with methanol and dichloromethane, to give the title compound (D31) as a yellow solid (152 mg, 38%) MH^+=296.

Description 32

2-[6-Amino-3-methoxy-2-(4-methylpiperazin-1-yl)phenyl]ethanol (D32)

The title compound (D32) was prepared from 2-[3-methoxy-2-(4-methylpiperazin-1-yl)-6-nitrophenyl]ethanol (D31) (142 mg, 0.48 mmol) using the method of Description 28 as a clear oil which crystallised on standing (94mg, 74%) MH^+=266.

Description 33

4-Methoxy-2-methyl-3-(4-methylpiperazin-1-yl)phenylamine (D33)

The title compound (D33) was prepared from 1-(6-methoxy-2-methyl-3-nitrophenyl)-4-methylpiperazine (D30) (150 mg, 0.56 mmol) using the method of Description 28 as a tan powder (78 mg, 59%) MH^+=236.

Description 34

1-(2-Methoxy-4-nitrophenyl)-4-methylpiperazine (D34)

A mixture of N-methylpiperazine (216 mg, 2.15 mmol), 2-bromo-5-nitroanisole (1g, 4.3 mmol), potassium carbonate (447 mg, 3.23 mmol), copper (I) bromide (86.6 mg, 0.30 mmol) in pyridine (0.5 ml) and toluene (2 ml) was heated at 100° C overnight. After cooling, the mixture was partitioned between water and ether and the aqueous phase was further extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure, to give the crude product. This was purified by chromatography on silica gel, eluting with methanol and dichloromethane, to give the title compound (D34) as a yellow/brown oil (80 mg, 15%) MH^+=252.

Description 35

3-Methoxy-4-(4-methylpiperazin-1-yl)phenylamine (D35)

The title compound (D35) was prepared from 1-(2-methoxy-4-nitrophenyl)-4-methylpiperazine (D34) (80mg, 0.319 mmol) using the method of Description 28 (50 mg, 71%) MH^+=222.

Description 36

4-(2-Methoxy-5-nitrophenyl)pyridine (D36)

A stirred mixture of 2-bromo-4-nitroanisole (7.6g, 32.7 mmol), 4-pyridineboronic acid (4.07g, 33 mmol) and powdered sodium carbonate (13.8g, 5 equivalents) in 1:1 1,2-dimethoxyethane: water (1,360 ml) was degassed for 0.5hr, by the passage of a

stream of argon. Tetrakistriphenylphosphine palladium (0) (1.35g) was added, and the mixture was cooled, the solvents evaporated under reduced pressure to approximately half-volume, and the aqueous residue was acidified with 5N hydrochloric acid and washed with ethyl acetate. The acid phase was then basified with solid potassium carbonate, and extracted into ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (D36) as a pale yellow solid (3.4g, 45%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.7 (d, 2H), 8.32 (d, 1H), 8.29-8.25 (m, 1H), 7.47 (d, 2H), 7.09 (d, 1H), 3.96 (s, 3H).

Description 37

4-(2-Methoxy-5-nitrophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (D37)

A solution of 4-(2-methoxy-5-nitrophenyl)pyridine (D36) (3.4g, 14.8 mmol) in acetone (150 ml) was treated with excess iodomethane (5 ml) and the mixture stirred at room temperature overnight. The precipitated quaternary salt was filtered off, washed with acetone and dried, giving 5.02g. This was dissolved in 1:1 ethanol: water (230 ml) and treated portionwise at room temperature, under argon, with sodium borohydride (1.23g, 32.4 mmol). The mixture was stirred for 1 h at room temperature then potassium carbonate (10 g) was added and the organic layer was separated from the aqueous phase, which was back-extracted with ethyl acetate. The organic phases were combined and dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (D37) as an orange oil, which slowly crystallised (3.05g, 91%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.15 (d, 1H), 8.05 (s, 1H), 6.9 (d, 1H), 5.9-5.84 (m, 1H), 3.9 (s, 3H), 3.15-3.05 (m, 2H), 2.7-2.61 (m, 2H), 2.6-2.5 (m, 2H), 2.4 (s, 3H).

Description 38

4-Methoxy-3-(1-methylpiperidin-1-yl)phenylamine (D38)

A solution of 4-(2-methoxy-5-nitrophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (D37) (1.0g, 4 mmol) in ethanol (50 ml) and glacial acetic acid (5 ml) was hydrogenated over 10% palladium on charcoal at 50°C and 50 psi for 4 days. The catalyst was removed by filtration, the filtrate evaporated under reduced pressure and the residue partitioned between potassium carbonate (aq) and dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (D38) as a brown oil which rapidly crystallised to a light tan powder (760 mg, 86%). MH^+=221.

Description 39

4-Methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenylamine hydrochloride (D39)

A solution of 4-(2-methoxy-5-nitrophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (D37) (570 mg, 2 mmol), in ethanol (35 ml), was warmed to 60°C and treated dropwise with a solution of stannous chloride (2g) in conc. hydrochloric acid (4 ml). The mixture was heated for a further 2 h after addition, and allowed to cool. The precipitate was filtered off, and washed with ethanol to give the title compound (D39) as a pale yellow powder (580 mg, 99%). MH^+=219.

General preparation of aryl-N-(4-methoxy-3-piperazin-1-yl)-benzenesulfonamide hydrochlorides on solid phase

Description 40

Preparation of 1-(2-methoxy-5-nitrophenyl)piperazin-4-yl bound to Merrifield resin

A solution of 1-(2-methoxy-5-nitrophenyl)piperazine (9.7g) in N-methylpyrrolidin-2-one (NMP) (150ml) was heated with chloromethylpolystyrene-divinylbenzene resin (Merrifield, 150-300 mesh) at 60°C for 24h under argon. The resin was then filtered, washed (NMP; dichloromethane/methanol gradient) and dried to give the title compound (6.9g) which was used directly in Description 41.

Description 41

Preparation of 1-(5-amino-2-methoxyphenyl)piperazin-4-yl bound to Merrifield resin

A solution of stannous chloride dihydrate (9g) in N,N-dimethylformamide (DMF) (120ml) was stirred for 72h at room temperature under argon with the resin from Description 40 (6.9g). The resin was filtered, washed (DMF; dichloromethane/methanol gradient) and dried to give the title compound (6.6g) which was used directly in Description 42.

Description 42

General preparation of aryl-N-(4-methoxy-3-(4-polymerylpiperazin-1-yl)-benzenesulfonamide bound to Merrifield resin

A solution of aryl sulfonyl chloride (0.4mmol) and di-isopropylethylamine (1mmol) in dichloromethane (3ml) was agitated for 24h at room temperature with the resin (0.1 mmol) from Description 41. The resin was then filtered, washed (dichloromethane;

dichloromethane/methanol gradient; methanol) to yield the title compound which was used directly in Examples 133-137.

Description 43

(S)-1-Methyl-2-(2-methoxy-5-nitrophenoxy)-pyrrolidine (D43)

A solution of 2-methoxy-5-nitrophenol (5.58g; 0.033mol), (S)-1-methyl-2-hydroxymethylpyrrolidine (3.45g; 0.03mol) and triphenylphosphine (8.65g; 0.033mol) in dry THF (80ml) was cooled to 5° and treated with DEAD (5.2ml; 0.033mol) over 15min. The reaction mixture was allowed to stand at RT for 16h, then evaporated in vacuo and partitioned 5%NaOH(aq)/Et2O. The organic phase was separated and extracted with 10%HCl(aq). The aqueous extract was washed with Et2O, basified with 40%NaOH(aq) and extracted with Et2O. The organic extracts were washed with H2O, dried over Na2SO4 and evaporated in vacuo to yield the title compound (D43) (6.79g; 85%) $MH^+ = 267$.

Description 44

(S)-1-Methyl-2-(2-methoxy-5-aminophenoxy)pyrrolidine (D44)

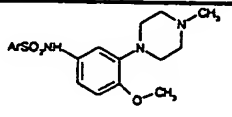
A solution of (S)-1-methyl-2-(2-methoxy-5-nitrophenoxy)pyrrolidine (D43) (6.79g;0.0255mol) in ethanol (200ml) was hydrogenated in the presence of 5%Pd/C catalyst (0.5g added as an aqueous slurry) at atmospheric pressure and RT for 16 hours. The catalyst was removed by filtration through kieselguhr and the filtrate evaporated in vacuo to yield the title compound (D44) (5.64g; 93%) MH^+=237.

Example 1

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]thiophene-2-ylsulfonamide

A solution of thiophene-2-sulfonyl chloride (82mg;0.45mmol) in acetone (2ml) was added to a solution of 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (100mg;0.45mmol) in acetone (2ml) and the mixture stood overnight at room temperature. The resultant crystalline solid was filtered off and washed with acetone, then diethyl ether, to afford the title compound as the hydrochloride salt. (153mg;84%). MS: m/z = 368.

The following compounds were prepared in a similar manner.

	MS (MH+)
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E2)	441

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide (E3)	368
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-5-(pyridin-2-yl)-2-thiophenesulfonamide (E4)	445
2,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-thiophenesulfonamide (E5)	436/438
4-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide (E6)	482
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E7)	362
3-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide (E8)	480/482
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzylsulfonamide (E9)	376
2-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E10)	440/442
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E11)	440/442
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide (E12)	410
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-*trans*-styrenesulfonamide (E13)	388
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E14)	430
3,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E15)	430/432
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-[2,1,3]benzothiadiazole-4-sulfonamide (E16)	420
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-2-benzothiophenesulfonamide (E17)	466
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-5-nitro-benzenesulfonamide (E18)	421
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-trifluoromethyl-benzenesulfonamide (E19)	430
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-trifluoromethyl-benzenesulfonamide (E20)	430
2,5-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-	422

benzenesulfonamide (E21)	
4-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E22	380
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E23)	396
4-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E24)	488
4-Ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E25)	390
4-*tert*-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E26)	418
4-Isopropyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E27)	404
4-*tert*-Amyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E28)	432
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-trifluoromethoxy-benzenesulfonamide (E29)	446
4-n-Butoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E30)	434
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methylbenzenesulfonamide (E31)	376
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide (E32)	402
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide (E33)	412
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-naphthalenesulfonamide (E34)	412
5-(Dimethylamino)-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide (E35)	455
4-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-benzenesulfonamide (E36)	452/454
4-Methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E37)	392
4-n-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E38)	418
4-Amino-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E39)	377

2-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E40)	396
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E41)	396
2,3,4-Trichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E42)	464/466
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,5-dimethyl-benzenesulfonamide (E43)	424
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzenesulfonamide (E44)	376
2,5-Dibromo-3,6-difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E45)	556
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,3,5,6-tetramethyl-benzenesulfonamide (E46)	418
5-Chloro-2-methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E47)	426
3-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E48)	380
3,4-Difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E49)	398
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-nitro-benzenesulfonamide (E50)	441
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-benzenesulfonamide (E51)	410
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-8-quinolinesulfonamide (E52)	413
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenylbenzenesulfonamide (E53)	438
3,4-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E54)	374
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,5-dimethyl-4-isoxazolesulfonamide (E55)	381
4-Bromo-N-[4-methoxy-3-(4-ethylpiperazin-1-yl)phenyl]benzenesulfonamide (E56)	454/456
2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E57)	430
5-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-	502

benzenesulfonamide (E58)	
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide (E59)	488
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide (E60)	502
5-Chloronaphthalene-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E61)	446
5-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E62)	446
4-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E63)	446
7-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E64)	446
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E65)	466
Benzofuran-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E66)	402
1-Methyl-1H-indole-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide (E67)	415
2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E138)	430/432

Preparation of Aryl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzene sulfonamides

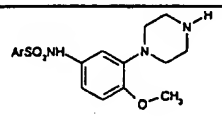
These compounds were prepared using one of the three general methods as outlined below.

General Method 1

Examples 68-75 were prepared by the following general method from the corresponding N-methyl piperazine analogues:

A solution of 1-chloroethylchloroformate (1.7mmol) and the appropriate N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-arylsulfonamide (0.34mmol) in 1,2-dichloroethane (4ml) was refluxed for 0.75h, cooled, diluted with diisopropylethylamine (1.7mmol) and refluxed for a further 2.5hrs. The solution was concentrated to a residue which was re-dissolved in methanol, refluxed for 1hr and then stirred at room temperature for 24h. The mixture was concentrated, and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate solution.

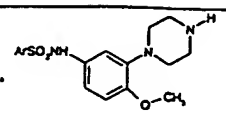
The organic layer was dried, concentrated to a residue and purified by column chromatography on silica gel using a methanol/dichloromethane solvent gradient. The hydrochloride salt of the product was prepared by dissolving the pure material from chromatography in acetone/dichloromethane and acidifying with ethereal HCl.

	$MS(MH^+)$
5-Pyridin-2-ylthiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E68)	431
N-(4-Methoxy-3-piperazin-1-ylphenyl)-3-trifluoromethylbenzenesulfonamide (E69)	416
3-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E70)	474
3,5-Dimethylisoxazole-4-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E71)	367
3,5-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E72)	416/418
2,5-Dibromo-3,6-difluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E73)	542
Naphthalene-1-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E74)	398
2-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E75)	466/468

General Method 2

Examples 76-86 were prepared by the following general method from the appropriate N-Boc derivative (D4-D14):

A stirred solution of the appropriate N-Boc derivative (D4-D14) (10.3mmol) in methanol (100ml) and 1M ethereal HCl (51.6ml) was heated at 60°C for 1.5h. The mixture was then concentrated and the residue stirred with acetone to afford the following title compounds as the hydrochloride salts.

	MS(MH^+)
2-Chloro-4-fluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E76)	400/402
3-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E77)	426/428
3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E78)	382/384
5-Chloronaphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide (E79)	432/434
4-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E80)	466/468
2,5-Dichlorothiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E81)	422/424
4-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E82)	426
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E83)	452
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E84)	452
1-Methyl-1H-indole-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E85)	401
Benzofuran-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (E86)	388

Example 83

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl)amide hydrochloride (E83)

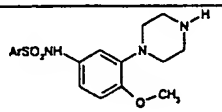
A stirred suspension of 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenylamide (D10) (193g) in tetrahydrofuran (820ml) and concentrated hydrochloric acid (180ml) was heated at reflux for 1.75h after which time a solution was obtained. The solution was concentrated and the residue dissolved in hot ethanol (600ml). Upon cooling, a solid precipitated which was filtered and recrystallised (ethanol/water 1:1) to give the title compound (E83) as a white solid, m.p. 276-280°C (dec.) (142g, 83%). δ_H (250 MHz, D6-dmso) 2.29 (3H, s), 2.90 (4H, br s), 3.01 (4H, br s), 3.55 (3H, s), 6.54-6.71 (3H,

m), 7.42 (1H, d, J 8.8Hz), 7.85 (1H, s), 7.93 (1H, d, J 8.8Hz), 9.03 (2H, br s), 10.3 (1H, br s). MH^+ 452.

General Method 3

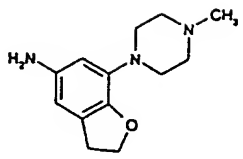
Examples 87-94 were prepared by the following general method:

A solution of the appropriate arylsulfonyl chloride (0.47mmol) and the aniline from D16 (0.47mmol) in dichloromethane (4ml) and pyridine (2.4mmol) was stirred for 18h at room temperature. The mixture was washed with 1M aqueous HCl then water. The layers were separated and to the organic one was added 4.4M aqueous KOH (1.4mmol) with vigorous stirring for 18h. To the heterogeneous mixture was then added an equal volume of 10% phosphate buffer. The layers were again separated and the organic phase was dried and diluted with 1M ethereal HCl to afford the hydrochloride salts of the following compounds as a precipitate.

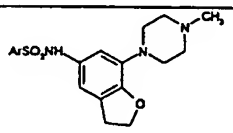
	MS(MH^+)
Naphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide (E87)	398
5-Chloronaphthalene-1-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide (E88)	432/434
4-Chloro-2,5-dimethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E89)	410/412
3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E90)	416/418
3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-4-methyl-benzenesulfonamide (E91)	396/398
2-Trifluoromethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E92)	416
4-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E93)	474
4-tert-Butyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide (E94)	404

Examples 95-108

The dihydrobenzofuran derivative, below,



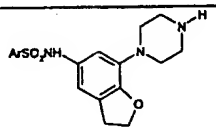
was prepared as described previously WO 95/11243 (Glaxo) and coupled with the appropriate aryl sulfonyl chlorides in the manner described in Example 1 to afford the following compounds:

	MS(MH^+)
Naphthalene-1-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E95)	424
Thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E96)	380
5-Chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E97)	414/416
5-Pyridin-2-ylthiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E98)	457
2,5-Dichlorothiophene-3-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E99)	448/450
4-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E100)	492/494
3-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E101)	492/494
4-Chloro-2,5-dimethyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide (E102)	436
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E103)	478
Naphthalene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide (E104)	424
3-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide (E105)	452/454

3,5-Dichloro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide (E106)	442/444
4-*tert*-Butyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide (E107)	430
2,5-Dibromo-3,6-difluoro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide (E108)	568

Examples 109-110

The following compounds were prepared from the corresponding N-methyl analogues by the general method described for Examples 68-75:

	$MS(MH^+)$
2,5-Dibromo-3,6-difluoro-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzenesulfonamide (E109)	554
4-Chloro-2,5-dimethyl-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzenesulfonamide (E110)	422

Example 111

5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [3-(4-cyclopropylmethyl-piperazin-1-yl)-4-methoxy-phenyl] amide (E111)

To a solution of 3-(4-benzyl-piperazin-1-yl)-4-methoxy-phenylamine (D22) (1mmol) in acetone (5ml) was added 5-chloro-3-methylbenzothiophene-2-sulphonyl chloride (1mmol). Stirring was continued at room temperature for 14hrs. The hydrochloride salt of the sulphonamide was collected by filtration, triturated with diethyl ether and dried *in vacuo* in 42% yield. Found MH^+ 506 / 508.

Example 112

5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [3-(4-benzyl-piperazin-1-yl)-4-methoxy-phenyl]-amide (E112)

The title compound was prepared in 32% yield using the procedure outlined for E111. Found MH^+ 542 / 544

Example 113

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (E113)

To a suspension of boron tribromide dimethyl sulphide complex (620mg, 2mmol) in 1,2 dichloroethane (30ml) under argon was added 5-chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]amide (E17) (0.2mmol). The reaction mixture was heated to reflux for 12hrs, cooled, quenched by the addition of water (20ml) and partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the title compound (E113). Found MH^+ 452 / 454

General Method for the Preparation of Examples 114-116

A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (E113) (100mg, 0.22mmol) and 18-Crown-6 (58mg, 0.22mmol) in DMF (0.5ml) was added to potassium hydride (35% dispersion in mineral oil, 50mg, 0.44mol) at room temperature under argon. After 10minutes a solution of the alkylating agent (0.22mmol) in DMF (0.3ml) was added and stirring was continued for 12 hrs. The reaction mixture was quenched with water and then concentrated in vacuo before partitioning between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography on silica to afford the following alkylated final compounds.

Example 114

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-benzyloxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (E114)

Prepared in 22% yield using benzyl bromide. Found MH^+ 542 / 544.

Example 115

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-ethoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (E115)

Prepared in 28% yield using the procedure outlined above using ethyl iodide. Found MH^+ 480 / 482.

Example 116

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-isopropoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (E116)

Prepared in 20% yield using the procedure outlined above using 2-iodopropane. Found MH^+ 494 / 496.

Example 117

5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-methoxy-3-(1-methyl-pyrrolidin-3-yloxy)-phenyl]-amide (E117)

The title compound was prepared in 48% yield from D25 and 5-chloro-3-methylbenzothiophene-2-sulphonyl chloride as described for E111. Found MH^+ 467 / 469.

Example 118

Naphthalene-2-sulfonic acid [2-bromo-5-(4-methylpiperazin-1-yl)phenyl]amide (E118)

The title compound (E118) was prepared from naphthalene-2-sulfonyl chloride (100 mg, 0.44 mmol) and 2-bromo-5-(4-methylpiperazin-1-yl)phenylamine (D27) (120 mg, 0.44 mmol) using the method of Example 1 (85 mg, 35%) MH^+=460/462.

Example 119

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-chloro-3-(4-methylpiperazin-1-yl)phenyl]amide (E119).

The title compound (E119) was prepared from 4-chloro-3-(4-methylpiperazin-1-yl)benzenamine (EP 0533267A, intermediate 42) (50 mg, 0.22 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (62 mg, 0.22 mmol) using the method of Example 1 (49 mg, 44%) MH^+=470/472.

Example 120

Naphthalene-2-sulfonic acid [4-bromo-3-(4-methylpiperazin-1-yl)phenyl]amide (E120)

The title compound (E120) was prepared from 4-bromo-3-(4-methylpiperazin-1-yl)benzenamine (EP 0533267A, intermediate 61) (600 mg, 2.23 mmol) and naphthalene-2-sulfonyl chloride (504 mg, 2.23 mmol) using the method of Example 1 (939 mg, 92%) MH^+=460/462.

Example 121

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[3-(2-dimethylaminoethoxy)-4-iodophenyl]amide (E121).

The title compound was prepared from 3-(2-dimethylaminoethoxy)-4-iodoaniline (WO95/15954, Description 50) (109mg, 0.36 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (100 mg, 0.36 mmol) using the method of Example 1 (70 mg, 36%) MH^+=551/553.

Example 122

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-dimethylaminoethyl)-2,3-dihydro-1H-indol-6-yl]amide (E122)

The title compound (E122) was prepared from 1-(2-dimethylaminoethyl)-2,3-dihydro-1H-indol-6-ylamine (WO95/32967 Description 4) (100 mg, 0.49 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (137 mg, 0.49 mmol) using the method of Example 1 (40g, 18%) MH^+=450/452.

Example 123

1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole (E123)

The title compound (E123) was prepared from 6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole (prepared from 3-nitroaniline, using methodology of WO95/06637 Intermediate 3) (39 mg, 0.18 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (50 mg; 0.18 mmol) using the method of Example 1 (75 mg, 84%) MH^+=462/464.

Example 124

1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole (E124)

The title compound (E124) was prepared from 5-methoxy-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole (WO95/06637 intermediate 3) (99 mg, 0.4 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (113 mg, 0.4 mmol) using the method of Example 1 (194 mg, 92%) MH^+=492/494.

Example 125

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[4-methoxy-2-methyl-3-(4-methylpiperazin-1-yl)phenyl]amide (E125)

The title compound (E125) was prepared from 4-methoxy-2-methyl-3-(4-methylpiperazin-1-yl)phenylamine (D33) (58 mg, 0.247 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (70 mg, 0.247 mmol) using the method of Example 1 (103 mg, 81%). MH^+=480/482.

Example 126

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[2-(2-hydroxyethyl)-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (E126)

The title compound (E126) was prepared from 2-[6-amino-3-methoxy-2-(4-methylpiperazin-1-yl)phenyl]ethanol (D32) (74mg, 0.28 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (78 mg, 0.28 mmol) using the method of Example 1 (18 mg, 13%). MH^+=510.

Example 127

1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-4-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole hydrochloride (E127)

A mixture of 5-chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[2-(2-hydroxyethyl)-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (E126) (218 mg, 0.25 mmol) and triphenyl phosphine (183 mg, 0.375 mmol) in dry THF (5 ml) under argon, was treated with a solution of diethyl azodicarboxylate (110 mg, 0.375 mmol) in dry THF (5 ml). The mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and the residue partitioned between dilute hydrochloric acid and ethyl acetate. The acidic layer was basified with 40% sodium hydroxide and re-extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product, which was purified by chromatography on silica gel, eluting with methanol and dichloromethane and the hydrochloride salt was formed (52 mg, 23%) MH^+=492/494.

Example 128

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[3-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amide (E128)

A solution of 3-methoxy-4-(4-methylpiperazin-1-yl)phenylamine (D35) (50 mg, 0.23 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (64 mg, 0.23 mmol) in dichloromethane (2 ml) was allowed to stand at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with potassium carbonate (aq), which was back-extracted with further dichloromethane. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product, which was purified by chromatography on silica gel, eluting with methanol and dichloromethane. This gave the title compound (E128) as an off-white solid (36 mg, 34%) MH^+=466.

Example 129

4-Bromo-N-[4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]benzenesulfonamide (E129)

The title compound (E129) was prepared from 4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenylamine (free base of D39) (107 mg; 0.49 mmol) and 4-bromobenzenesulfonylchloride (125 mg, 0.49 mmol) using the method of Example 1 (179 mg, 77%) MH^+=437/439.

Example 130

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]amide (E130)

The title compound (E130) was prepared from 4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenylamine (free base of D39) (100 mg, 0.46 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (129 mg, 0.46 mmol) using the method of Example 1 (177 mg, 77%). MH^+=463/465.

Example 131

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methylpiperidin-4-yl)phenyl]amide (E131)

The title compound (E131) was prepared from 4-methoxy-3-(1-methylpiperidin-1-yl)phenylamine (D38) (150 mg, 0.68 mmol) and 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride (192 mg, 0.68 mmol) using the method of Example 1 (108 mg, 32%) MH^+=465/467.

Example 132

Naphthalene-2-sulfonic acid [3-(4-methylpiperazin-1-yl)phenyl]amide (E132)

The title compound (E132) was prepared from 3-(4-methylpiperazin-1-yl)benzenamine and naphthalene-2-sulfonyl chloride according to the method of Example 1 MH^+=382.

Preparation of aryl-N-(4-methoxy-3-piperazin-1-yl)-benzenesulfonamide hydrochlorides on solid phase (Examples 133-137)

The resin from Description 42 was stirred for 24h at room temperature with a solution of 1-chloroethylchloroformate (1.1mmol) in dichloromethane (2ml) then filtered and washed with dichloromethane. The filtrate was concentrated and the residue redissolved in methanol (3ml) and the solution refluxed for 5h. The solution was then concentrated to yield the title compound.

The following compounds were prepared as described above:

compound	MH^+
2,3,4-Trichloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)benzenesulfonamide (E133)	450/452
2,3-Dichloro-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide (E134)	416/418
3-Chloro-2-methyl-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide (E135)	396/398
4-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide (E136)	382/384
5-Bromo-thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-yl-phenyl)-amide (E137)	432/434

Example 138

2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide (E138) MS(MH+) 430/432 was prepared according to the general method of Example 1

Examples 139-141

The following compounds were prepared in an analagous way to Examples 68-75

	MS(MH+)
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-phenyl-6-piperazin-1-yl-2,3-dihydro-1H-indole (E139)	524/526
5-Chloro-1-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-6-piperazin-1-yl-2,3-dihydro-1H-indole (E140)	482/484
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-7-piperazin-yl-1,2,3,4-tetrahydroquinoline (E141)	462/464

Example 142

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]amide (E142)

The title compound (E142) was prepared from 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride and 4-methyl-3-(4-methylpiperazin-1-yl)benzenamine according to the method of Example 1 $MH^+ = 448/450$.

Example 143

(S)-5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid[4-methoxy-3-(1-methylpyrrolidin-2-ylmethoxy)phenyl]amide (E143)

A solution of (S)-1-methyl-2-(2-methoxy-5-aminophenoxy)pyrrolidine (D44) (0.22g;$9.3x10^{-4}$ mol) in DCM (10ml) containing DIPEA (0.162ml;$9.3x10^{-4}$ mol) was treated with 5-chloro-3-methylbenzene-2-sulphonyl chloride (0.262;$9.3x10^{-4}$ mol) portionwise. Stirred at RT for 18h, then evaporated *in vacuo* and the residue purified by Sep-Pak Silica-gel column chromatography with 2%MeOH/DCM as eluent to yield the title compound as a clear, colourless gum (0.14g; 31%). This was converted to the hydrochloride salt with HCl in Et2O (0.31ml of a 1.0M solution) with trituration yielding the title compound (E143) as the salt as a white, crystalline solid (0.13g) $MH^+ = 481/483$.

Method for assay of 5-HT6 antagonistic activity:

The test compounds were dissolved in polyethylene glycol:dimethyl sulphoxide (1:1) at 1 or 10mM and diluted to 0.1mM using 5mM tris buffer (pH 7.7 @ 25°C). Dissolution was assisted by addition of 0.02ml 5M HCl plus heating to 40°C and sonication for 10 minutes. Serial dilutions of drugs in the same buffer were carried out using either a TECAN 5052 or Biomek 2000 Workstation. Samples of the diluted test compounds (0.05ml) were mixed with 0.05ml of radio-ligand [^{3}H]-LSD prepared in the incubation buffer, and 0.4ml of a suspension of a preparation of the washed membranes of HeLa_5HT6 cells (acquired from Dr. D. Sibley, NIH, Bethesda, see Ref 1)(see Table 1), also in the incubation buffer. The details of the incubation conditions for each assay are shown in Table 2. The incubation buffer was 50mM Trizma (Sigma, UK) pH7.7 @ 25°C, 4mM $MgCl_2$.

After incubation at 37°C, the mixtures were filtered using a Packard Filtermate in Packard TopCount format. Filters were washed with 4 x 1ml aliquots of ice-cold incubation buffer. Filters were dried and impregnated with 0.04ml of Microscint 20 (Packard). IC_{50} values were estimated from the counts per minute using a four parameter logistic curve fit within EXCEL (2). K_i values were calculated using the method of Cheng and Prusoff (3). pIC_{50} and pK_i are the negative log10 of the molar IC_{50} and K_i respectively.

Table 1 Details of the methods used to prepare membranes for binding assays

1st resuspension cells/ml	spin / resuspension 1, 2 ,3	Incubation before final spin	protein conc. in stored aliquots	cells /ml in stored aliquots
7×10^7	Yes	20min at 37°C	4mg/ml	1.0×10^8

Table 2 Summary of receptor binding assay conditions

protein (ug/ sample)	radio-ligand [^{3}H]-LSD (nM)	Specific Activity (Ci/mmol)	Non-Specific Definition	Kd (nM)
40	2.0	83	Methiothepin	3.1

References

1. MONSMA, F.J., SHEN, Y., WARD, R.P., HAMBLIN, M.W., SIBLEY, D.R.. 1993. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.*, **43**, 320-327.

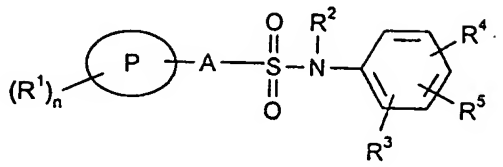
2. BOWEN, W.P., JERMAN, J.C.. 1995. Nonlinear regression using spreadsheets. *Trends in Pharmacol. Sci.*, **16**, 413-417.

3. CHENG, Y.C., PRUSSOF, W.H.. 1973. Relationship between inhibition constant (Ki) and the concentration of inhibitor which causes 50% inhibition (IC50) of an enzymatic reaction. *Biochem. Pharmacol.*, **92**, 881-894.

The compounds of Examples 11, 15, 17, 61, 65, 70, 72, 77, 78, 79, 83, 84, 87 and 90 all showed particularly good selective 5-HT6 receptor antagonist activity, having pKi values above 8.0 at human cloned 5-HT6 receptors.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, amino, alkylamino or dialkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6:

R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-C_{1-6} -alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano or aryl.

2. A compound according to claim 1 in which P is phenyl, thiophene, benzothiophene or naphthyl.

3. A compound according to claim 1 or 2 in which R^1 is halogen or C_{1-6}alkyl optionally substituted by one or more halogen atoms.

4 A compound according to any one of claims 1 to 3 in which R^2 is hydrogen

5 A compound according to any one of claims 1 to 4 in which R^4 is an optionally substituted piperazine ring.

6. A compound according to any one of claims 1 to 5 in which R^4 is an unsubstituted piperazine ring.

7. A compound according to any one of claims 1 to 6 in which R^5 is C_{1-6}alkoxy.

8. A compound according to any one of claims 1 to 7 in which R^5 is para with respect to the sulphonamide linkage.

9. A compound according to any one of claims 1 to 8 in which P-A is 5-chloro-3-methyl-benzo[2]thiophen-2-yl.

10. A compound according to claim 1 which is:
4-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-5-(pyridin-2-yl)-2-thiophenesulfonamide,
2,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-thiophenesulfonamide,
4-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Bromo-5-chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzylsulfonamide,
2-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-*trans*-styrenesulfonamide,
3,4-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3,5-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-[2,1,3]benzothiadiazole-4-sulfonamide,
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-2-benzothiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-5-nitro-benzenesulfonamide,

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-trifluoromethyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-trifluoromethyl-benzenesulfonamide,
2,5-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
4-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Ethyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-*tert*-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Isopropyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-*tert*-Amyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-trifluoromethoxy-benzenesulfonamide,
4-n-Butoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methylbenzenesulfonamide,
5-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-thiophenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-naphthalenesulfonamide,
5-(Dimethylamino)-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-1-naphthalenesulfonamide,
4-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-benzenesulfonamide,
4-Methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-n-Butyl-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Amino-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
2-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
2,3,4-Trichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,5-dimethyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methylbenzenesulfonamide,
2,5-Dibromo-3,6-difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2,3,5,6-tetramethyl-benzenesulfonamide,

5-Chloro-2-methoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
3-Fluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3,4-Difluoro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
4-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-nitro-benzenesulfonamide,
3-Chloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-8-quinolinesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenylbenzenesulfonamide,
3,4-Dimethoxy-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3,5-dimethyl-4-isoxazolesulfonamide,
4-Bromo-N-[4-methoxy-3-(4-ethylpiperazin-1-yl)phenyl]benzenesulfonamide,
2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
5-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-benzenesulfonamide,
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide,
3-Iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-methyl-benzenesulfonamide,
5-Chloronaphthalene-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
4-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
7-Chloronaphthalene-1-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
Benzofuran-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
1-Methyl-1H-indole-2-sulfonic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] amide,
5-Pyridin-2-ylthiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
N-(4-Methoxy-3-piperazin-1-ylphenyl)-3-trifluoromethylbenzenesulfonamide,
3-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3,5-Dimethylisoxazole-4-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,

3,5-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
2,5-Dibromo-3,6-difluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzene-sulfonamide,
Naphthalene-1-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
2-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
2-Chloro-4-fluoro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
5-Chloronaphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,
4-Bromo-5-chlorothiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
2,5-Dichlorothiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide
4-Bromo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
5-Chloro-2-methylbenzo[b]thiophene-3-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
1-Methyl-1H-indole-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
Benzofuran-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide,
Naphthalene-2-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,
5-Chloronaphthalene-1-sulfonic acid(4-methoxy-3-piperazin-1-ylphenyl)amide,
4-Chloro-2,5-dimethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3,4-Dichloro-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
3-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-4-methyl-benzenesulfonamide,
2-Trifluoromethyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
4-Iodo-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
4-Tert-butyl-N-(4-methoxy-3-piperazin-1-ylphenyl)benzenesulfonamide,
Naphthalene-1-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
Thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
5-Chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
5-Pyridin-2-ylthiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
2,5-Dichlorothiophene-3-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,

4-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
3-Bromo-5-chlorothiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
4-Chloro-2,5-dimethyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide,
Naphthalene-2-sulfonic acid [7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl] amide.
3-Bromo-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzene-sulfonamide,
3,5-Dichloro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzene-sulfonamide,
4-*Tert*-Butyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzene-sulfonamide,
2,5-Dibromo-3,6-difluoro-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzenesulfonamide,
2,5-Dibromo-3,6-difluoro-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzene-sulfonamide,
4-Chloro-2,5-dimethyl-N-(7-piperazin-1-yl-2,3-dihydrobenzofuran-5-yl)benzene-sulfonamide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [3-(4-cyclopropylmethyl-piperazin-1-yl)-4-methoxy-phenyl] amide
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [3-(4-benzyl-piperazin-1-yl)-4-methoxy-phenyl]-amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [4-hydroxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-benzyloxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [4-ethoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [4-isopropoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [4-methoxy-3-(1-methyl-pyrrolidin-3-yloxy)-phenyl]-amide,
Naphthalene-2-sulfonic acid [2-bromo-5-(4-methylpiperazin-1-yl)phenyl]amide,

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-chloro-3-(4-methylpiperazin-1-yl)phenyl]amide,
Naphthalene-2-sulfonic acid [4-bromo-3-(4-methylpiperazin-1-yl)phenyl]amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid[3-(2-dimethylaminoethoxy)-4-iodophenyl]amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [1-(2-dimethylaminoethyl)-2,3-dihydro-1H-indol-6-yl]amide,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-6-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-indole
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-2-methyl-3-(4-methylpiperazin-1-yl)phenyl]amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [2-(2-hydroxyethyl)-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-methoxy-4-(4-methyl-piperazin-1-yl)-2,3-dihydro-1H-indole hydrochloride,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [3-methoxy-4-(4-methyl-piperazin-1-yl)phenyl]amide,
4-Bromo-N-[4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]benzene-sulfonamide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]amide,
5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3-(1-methylpiperidin-4-yl)phenyl]amide,
Naphthalene-2-sulfonic acid [3-(4-methylpiperazin-1-yl)phenyl]amide,
2,3,4-Trichloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)benzenesulfonamide,
2,3-Dichloro-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide,
3-Chloro-2-methyl-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide,
4-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl) benzenesulfonamide,
5-Bromo-thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-yl-phenyl)-amide,
2,3-Dichloro-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-benzenesulfonamide,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-5-phenyl-6-piperazin-1-yl-2,3-dihydro-1H-indole,
5-Chloro-1-(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-6-piperazin-1-yl-2,3-dihydro-1H-indole,
1-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonyl)-7-piperazin-1-yl-1,2,3,4-tetrahydroquinoline,

5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methyl-3-(4-methylpiperazin-1-yl)phenyl]amide,
(S)-5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid [4-methoxy-3- (1-methylpyrrolidin-2-ylmethoxy)phenyl] amide,
and pharmaceutically acceptable salts thereof.

11. A compound according to any one of claims 1 to 9 which is 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide hydrochloride.

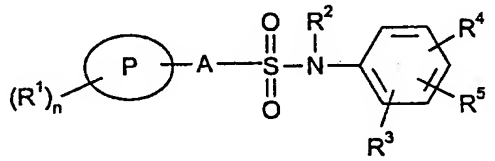
12. A compound according to any one of claims 1 to 11 for use in therapy.

13. A compound according to any one of claims 1 to 11 for use in therapy, in which the beneficial activity is effected by antagonism of 5-HT6 receptors.

14. A compound according to any one of claims 1 to 11 for use in the treatment of schizophrenia, Alzheimer's disease and/or depression.

15. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier or excipient.

16. A process for the preparation of a compound of formula (I) or a salt thereof:



(I)

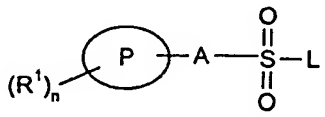
wherein:
P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;
R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, amino, alkylamino or dialkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
n is 0, 1, 2, 3, 4, 5 or 6:
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-C_{1-6} -alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

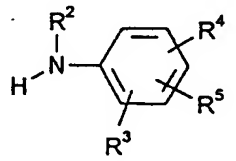
R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano or aryl,

which process comprises the coupling of a compound of formula (II):



(II)

in which R^1, n, P, and A are as defined in formula (I) or protected derivatives thereof and L is a leaving group with a compound of formula (III):



(III)

in which R^2, R^3, R^4 and R^5 are as defined in formula (I) or protected derivatives thereof and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 97/07159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D333/34 C07D295/135 C07D285/14 C07D307/79 C07D215/36
C07D209/30 C07D261/10 C07D333/62 C07D211/70 C07D409/04
C07D409/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 609 734 A (BAYER AG) 10 August 1994 see page 12, formula (I), page 28, last three compounds, page 29, page 30, first five compounds	1-4
X	WO 87 03782 A (FMC CORP.) 2 July 1987 see page 41a, formula; page 44, compounds 85-87	1-4

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[X] Further documents are listed in the continuation of box C.

[X] Patent-family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 1998	26/05/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	H. SAYO ET AL.: CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 25, no. 4, 1977, pages 640-6, XP002064436 see page 643, compound VIII	1,2
X	EP 0 558 999 A (BAYER AG) 8 September 1993 see claims 1-4	1
Y	WO 95 32967 A (SMITHKLINE BEECHAM PLC) 7 December 1995 cited in the application see page 1, line 3 see page 1, line 22 - line 23 see claims 1,9,10	1,12,15
Y	WO 95 06637 A (SMITHKLINE BEECHAM PLC) 9 March 1995 cited in the application see page 1, line 3 - line 9 see page 1, line 22 - line 23 see claims 1,9,10	1,12,15
Y	EP 0 533 267 A (GLAXO GROUP LTD.) 24 March 1993 cited in the application see claims 1,14,15	1,12,15
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Y	WO 95 15954 A (SMITHKLINE BEECHAM PLC) 15 June 1995 cited in the application see claims 1,9,10	1,12,15
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A	EP 0 021 580 A (J. A. WUELFING) 7 January 1981 cited in the application see claims 1,7	1,15

2

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Inte onal Application No
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